ence, as in the case of a uniform liquid globe (*11*). Nonetheless, the tendency toward phase mixing may generate large gradients in the radiative zone, which could lead to instabilities causing slow vertical mixing. It could be this process that leads to the lithium destruction that, as Howe *et al.* point out, is required to explain the depleted photospheric abundance of lithium. It seems most likely that the oscillations are driven by direct interaction with the convection, particularly because of the need to provide energy to compensate for the dissipation from phase mixing. Angular-momentum transfer by rotationally modulated gravity-wave dissipation in the stably stratified radiative zone also comes to mind, but this can hardly explain the high-latitude oscillation in the convection zone, unless it is somehow coupled to the equatorial oscillation. An alternative interpretation of the nature of the oscillations is that the observed signal is the axisymmetric signature of nonaxisymmetric nonlinear inertial oscillations in the convection zone, whose restoring force comes from vortex stretching. It is unlikely, however, that such modes could penetrate into the radiative interior without a magnetic connection.

These comments may contain the germ of an explanation of the new observations, but much is left unexplained. For example, why are there apparently independent oscillators at high and low latitudes? And why are the high-latitude oscillations apparently confined to the convection zone? The helioseismic inversions reported by Howe *et al.* provide only an average of the motion in the northern and southern hemispheres. The complexity of the high-latitude oscillations might therefore be partly a result of a superposition of two or more disconnected and somewhat different oscillators in the two hemispheres. One might also expect the amplitudes and perhaps the locations of the oscillations to vary over the sunspot cycle and possibly also to see a superposed solar-cycle oscillation in Ω. To address these and other pertinent issues, the observations must be extended over at least a whole 22-year cycle.

The principal lesson from these new results is that the sun is dynamically more active than often assumed. In common with previous discoveries about the internal rotation—such as the latitudinally propagating subphotospheric zonal flows, the anomalously slow polar rotation, and the possibly slowly rotating core—it was not anticipated. We must therefore regard with considerable caution any inference about the internal structure of the sun, or of any other star, that is derived from the presumption that radiative zones are quiescent.

References and Notes

1. N. O. Weiss, in *Lectures on Solar and Planetary Dynamos*, M. R. E. Proctor and A. D. Gilbert, Eds. (Cambridge Univ. Press, Cambridge, 1994), p. 59.
2. R. Howe *et al.*, *Science* **287**, 2456 (2000).
3. M. J. Thompson *et al.*, *Science* **272**, 1300 (1996).
4. E. A. Spiegel and J.-P. Zahn, *Astron. Astrophys.* **265**, 106 (1992).
5. D. O. Gough and M. E. McIntyre, *Nature* **394**, 755 (1998).
6. H. W. Babcock, *Astrophys. J.* **133**, 572 (1961).
7. Sunspots arise whatever the polarity of the solar magnetic field; alternate 11-year sunspot cycles have opposite polarity, yielding a 22-year magnetic cycle.
8. D. O. Gough *et al.*, in *Inside the Stars*, W. W. Weiss and A. Baglin, Eds., vol. 40 of Astronomical Society of the Pacific Conference Series (Astronomical Society of the Pacific, San Francisco, 1993), p. 304.
9. An Alfvén wave is a wave in the field lines that propagates at a speed proportional to the field strength and inversely proportional to the square root of the density of the material in which the field is embedded.
10. M. Venkatachalappa and A. M. Soward, *Geophys. Astrophys. Fluid Dyn.* **54**, 109 (1990).
11. T. G. Cowling, *Proc. R. Soc. London A* **233**, 219 (1955).
12. J. Schou *et al.*, *Astrophys. J.* **505**, 390 (1998).

PERSPECTIVES: STRUCTURAL BIOLOGY

Bit Players in the Trombone Orchestra

Peter H. von Hippel and Debra H. Jing

Semiconservative DNA replication, the process by which prokaryotes and eukaryotes copy their DNA, depends on the activity of enzymes called DNA polymerases. Two identical DNA polymerases operate at each "replication fork"—the moving junction of double-stranded DNA where two new strands of complementary DNA are made. One of the enzyme pair synthesizes the leading DNA strand and the other the lagging strand (see the figure). But how are the activities of the two DNA polymerases coordinated, and what tells them when to start and when to stop? This responsibility falls to a cadre of bit players (auxiliary replication proteins) that are essential to the success of the overall replication enterprise (*1, 2*). One of these bit players is the replication primase, and the molecular structure of its polymerase domain is described by Keck *et al.* (*3*) on page 2482 of this issue. This report and other recent biochemical and mechanistic studies (*4, 5*) shed light on how the primase and other replication factors interact with DNA polymerases and with one another to direct and coordinate DNA synthesis at the replication fork.

Coordinating the synthesis of the newly forming leading and lagging DNA strands is particularly difficult because the polarity of the DNA backbone dictates that polymerases can only synthesize DNA in one direction (that is, from the 5′ to the 3′ end). This means that the paired DNA polymerases at the replication fork must move in opposite directions along the two (antiparallel) DNA template strands. How they do this is best explained by the "trombone model" of replication (see the figure). In this model (*6*), looping-out of the lagging strand of template DNA permits the pair of DNA polymerases to synthesize the two new DNA strands in the same direction within the moving replication fork while actually moving in opposite directions along the template strands. To avoid the difficulties that would result from the generation of very long DNA loops, lagging-strand synthesis proceeds discontinuously, that is, through the production of short (one- to two-kilobase) pieces of single-stranded DNA (Okazaki fragments). This permits the periodic "resetting" of the loop of the trombone on the lagging strand, while leading-strand synthesis proceeds continuously. It is this functional asymmetry of the polymerases at the replication fork that provides both the opportunity and the need for the primase and other auxiliary proteins.

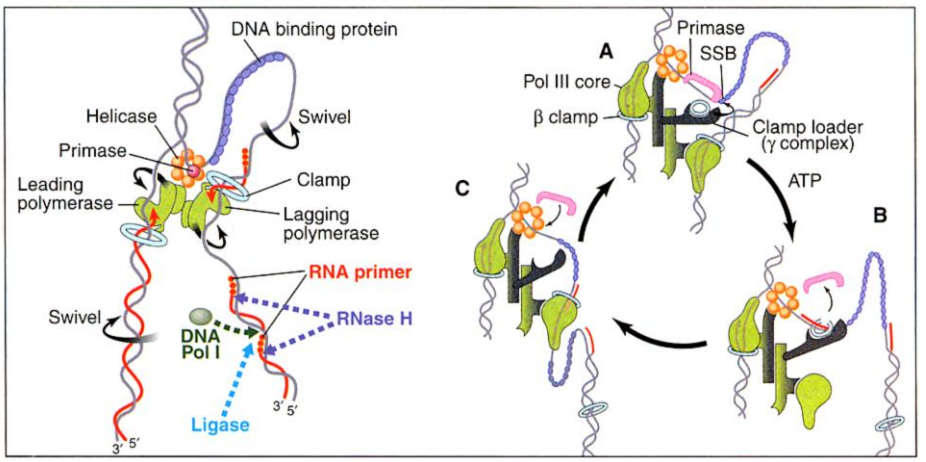
The primase is required because DNA polymerases cannot initiate DNA synthesis on their own; rather, they can only extend the 3′ end of a preexisting oligonucleotide that is hybridized to the DNA template strand. The primase takes care of this problem by synthesizing discrete RNA primers (11 nucleotides long in *Escherichia coli*) at defined positions on the DNA template. The DNA polymerase then extends the primers by synthesizing DNA. RNA priming need occur only once (at initiation) in leading-strand synthesis, but must occur repeatedly in the discontinuous synthesis of the lagging strand. [The RNA primers that are inserted into the newly forming lagging strand are subsequently removed by ribonuclease H and resynthesized against the template as DNA by another polymerase; breaks in the DNA backbone are sealed by DNA ligase (*1, 2*)].

The authors are at the Molecular Biology Institute, University of Oregon, Eugene, OR 97403, USA. E-mail: petevh@molbio.uoregon.edu, jing@molbio.uoregon.edu

There is some in vitro evidence to suggest that the primase may be recruited anew in each cycle of Okazaki fragment synthesis through interaction with the six-unit DNA helicase (DnaB in *E. coli*). The helicase has the double task of "opening" the double-stranded DNA ahead of the replication fork to expose the single-stranded DNA templates for synthesis and then simultaneously binding to and positioning the primase to initiate DNA synthesis (*7, 8*).

Although the primase is essential for DNA replication, little is known about its molecular architecture. Keck *et al.* (*3*) reveal the structure of the polymerase domain of the primase (in this case the central domain of DnaG in *E. coli*) and elucidate how RNA priming is controlled. It appears that the polymerase domain contains a cleft, narrow at one end and wider at the other, that is lined by several invariant acidic amino acids. This cleft flattens out into a shallow depression containing both basic and hydrophobic amino acids. The authors propose that the single-stranded DNA template is threaded through the narrow end of the cleft and that template-directed RNA synthesis is catalyzed through the transfer of phosphates by the conserved acidic residues in a metal ion–dependent reaction. The RNA-DNA hybrid sequence that is produced by the primase is then thought to be extruded into, and held within, the shallow depression of the polymerase domain. Interactions at this putative hybrid binding site may then serve to limit the progress of the primase and to control the size of the primer.

The primase of *E. coli* with its three essential domains may be small, but it is complex. The amino acids that constitute the polymerase domain are flanked on one side by an amino-terminal region whose zinc-finger motif may bind the recognition sequence of the DNA template. On the other side, the polymerase domain is flanked by a carboxyl-terminal region that interacts with the DNA helicase. These primase domains interact with the DNA of the replication fork and with the DNA helicase (*9*) to form a primosome complex that helps to control DNA synthesis as the replication fork moves.



A molecular trombone. The factors involved in the synthesis of the leading and lagging strands during DNA replication. The DNA polymerases of the leading and lagging strands, and the primase and helicase that operate at the replication fork are shown. The lagging strand is shown partially covered with SSB (single-stranded DNA binding) protein (**left, top**) and partially associated with RNA-primed Okazaki fragments (**left, bottom**). The sites of action of RNase H, DNA Pol I, and DNA ligase are shown. During lagging-strand synthesis there is a switch between primase and polymerase activity. (**A**) The six-subunit DnaB helicase encircling the lagging strand binds to the pair of DNA polymerases at the replication fork and to the primase, which synthesizes an RNA primer on the lagging strand. Each polymerase is tethered by a β processivity clamp, which is placed on the DNA by a γ clamp loader complex. (**B**) The χ subunit of the clamp loader interacts with SSB, breaking the primase-SSB contact and resulting in displacement of the primase. (**C**) Upon reconnecting with the DnaB helicase, the primase is then free to synthesize another RNA primer. [Adapted from (*4, 5*)].

In addition to their inability to initiate DNA synthesis, DNA polymerases are also unable to synthesize DNA processively (that is, to extend the growing DNA chain by many nucleotides before disengaging from the template) at physiological salt concentrations. This problem is overcome by the involvement of another bit player, the processivity clamp (assisted by an adenosine triphosphate–driven clamp-loading complex), which tethers the polymerase to the junction of the primer and the template within the moving replication fork (*10*). This allows leading-strand synthesis to proceed continuously. But how is this process interrupted to permit discontinuous priming and synthesis of the lagging strand?

The Keck study provides some "molecular flesh" for a recent model of lagging-strand synthesis (*4*). This model addresses three regulatory problems: (i) the coordination of the synthesis and stabilization of the RNA primer on the template DNA, (ii) the mechanism whereby the primed DNA is handed off to the DNA polymerase, and (iii) the loading of the processivity clamp to stabilize the primed template DNA–polymerase complex. The following mechanism has been proposed for this primase-to-polymerase switch (*4*). The completed RNA primer remains firmly in the grasp of the primase, which in turn is stabilized on the DNA template through contacts with the single-stranded binding protein (SSB in *E. coli*). Next, the χ subunit of the *E. coli* polymerase (pol III) binds to the same SSB protein, destabilizing the contacts between the primase and SSB and facilitating the assembly of the *E. coli* processivity clamp (β) onto the RNA primer–DNA template junction. Finally, the clamp binds and stabilizes the DNA polymerase on its DNA template, permitting processive synthesis of the lagging strand to continue until the next Okazaki fragment is reached. At this point, the clamp is released by the polymerase and continuous synthesis ceases. We note that SSB, which plays a number of important parts in the replication process (*1, 2*), also serves as the "pivot protein" in this hand-off process (see the figure) (*1, 2*).

Another recent study addresses additional mechanistic control problems in DNA replication (*5*). This study proposes a model to explain how torsional stress—hypothesized to develop in the DNA as a consequence of the spiral path taken around the DNA by the replication fork—is released because of the "looseness" with which the processivity clamp is bound to the DNA. Additional flexibility is afforded by the tethering of the polymerase to the clamp through the unstructured carboxyl-terminal "tail" of the enzyme. The combination of these two factors explains how the DNA might rotate within the clamp to relieve torsion without a complete displacement of the DNA polymerases from their template positions.

These elegant models, based in part on the emerging structures of the various solo and bit molecular players, illustrate the amazing progress that is under way in understanding the control of DNA replication.

References

1. T. A. Baker and S. P. Bell, *Cell* **92**, 295 (1998).
2. A. Kornberg and T. A. Baker, *DNA Replication* (Freeman, New York, ed. 2, 1992).
3. J. L. Keck *et al.*, *Science* **287**, 2482 (2000).
4. A. Yuzhakov *et al.*, *Cell* **96**, 153 (1999).
5. M. M. Hingorami and M. O'Donnell, *Curr. Biol.* **10**, R25 (2000).
6. B. M. Alberts *et al.*, *Cold Spring Harbor Symp. Quant. Biol.* **47**, 655 (1983).
7. H. Hiasa and K. J. Marians, *J. Biol. Chem.* **274**, 27244 (1999).
8. S. K. Johnson *et al.*, *Biochemistry* **39**, 736 (2000).
9. D. H. Jing *et al.*, *J. Biol. Chem.* **274**, 27287 (1999).
10. J. Kuriyan and M. O'Donnell, *J. Mol. Biol.* **234**, 915 (1993).